Sodium Intake and its association with Mortality in Chronic Kidney Disease patients

What is the relationship between dietary sodium intake and mortality in CKD patients?

M.J. Achterberg
5626285, Period P5&P6
R.W.M. Vernooij, D.M.J. Veltkamp
Department of Nephrology, Julius Center for Health Sciences and Primary Care

Abstract

Background & Aims: Current guidelines advise sodium restriction in all patients with chronic kidney disease (CKD). However, there is no direct evidence linking sodium intake to increased mortality. This study aims to investigate the relationship between sodium intake and mortality in CKD patients.
Methods: A retrospective cohort analysis, using routine clinical data from electronic healthcare records. Sodium intake was estimated by 24-hour urinary sodium excretion. Patients with a GFR of 15 to 60, with at least one 24-hour sodium excretion, visiting an outpatient clinic for dietetics and cardiovascular risk management were included. The association between sodium intake and mortality was investigated in two manners: 1) sodium intake as a continuous determinant; 2) sodium intake categorized as: low (i.e. < 100 mmol/day), middle (i.e. 100-200 mmol/day), and high (i.e. >200 mmol/day) intake. Cox proportional hazard analysis, adjusted for patient characteristics, kidney function and cardiovascular risk factors, was used to calculate hazard ratios time-varying sodium intake.
Results: In total, 3787 patients were included. 1268 patients were low-intake, 1966patients were mid-intake, 553 patients were high intake. Less than 33.5% of patients had a sodium intake below 100 mmol (equivalent to 5 grams of salt) per day. In the low sodium intake group, 38% of patients died, versus 22.1% in the high intake group. The corrected hazard ratios for mortality were 0.63 (95% CI: 0.55 – 0.72) for medium sodium intake and 0.68 (95% CI: 0.55 – 0.83) for high sodium intake. This hazard ratio accounts for varying levels of sodium intake over time.
Conclusions
Very low sodium intake is correlated with mortality, irrespective of kidney function. Furthermore, adherence to sodium guidelines is not possible for most patients. Sodium restriction should not be prescribed to all CKD patients. Rather, a personalised approach should be taken by doctors, dieticians, and patients.

Introduction

Chronic Kidney Disease (CKD) is a widely prevalent progressive condition responsible for approximately three percent of all global deaths each year[1]. It is expected to be the fifth most common cause of death by 2040[2]. Most CKD patients do not die of kidney failure, but of cardiovascular disease[3]. Hence, patients with CKD require a life-long cardiovascular risk management to mitigate their cardiovascular risk.

Hypertension is a cause of CKD and is associated with CKD progression[4]. Dietary sodium intake has been proven to induce a temporary increase in blood pressure by increasing extracellular volume[6]. This temporary increase in blood pressure lasts longer in CKD patients because of the decreased ability to excrete the sodium [6]. In theory, decreasing sodium intake should improve the patients' prognosis by lowering blood pressure [5,6, 7]. Therefore, current guidelines for management of CKD advise patients to limit dietary sodium intake to two grams of sodium (equivalent to five grams of salt) per day[8,9].

A systematic review including randomized controlled trials showed that stricter blood pressure control in CKD patients prevents disease progression and ESKD, but does not impact cardiovascular morbidity or mortality[10]. Meta-analyses of both retrospective cohort studies and RCTs combined in the patients with CKD showed mixed results but suggest a U-shaped relationship between sodium intake and mortality[11–13]. On the one hand a sodium restricted diet could lead to restriction of food intake in general, leading to malnutrition, or a total sodium deficiency causing recurrent hyponatremia[6], while a salt-rich diet could lead to hypertension. As of yet, the relationship between sodium intake and mortality within patients with CKD remains unclear. This paper aims to investigate the relationship between sodium intake and mortality and ESKD, stratified by renal function, in a cohort of 3787 patients with non-dialysis CKD seen in clinical practice, almost doubling the amount of currently available retrospective evidence in the non-dialysis CKD population[12,14–17].

Methods

Study Design & Patient Population

A retrospective cohort analysis was performed on data collected by the Utrecht Patient Oriented Database (UPOD)[18]. This database stores all available patient and clinical factors of all patients of the University Medical Centre Utrecht, a tertiary hospital in the Netherlands. We selected adult patients (18 years or older) who attended the outpatient clinic of the dietetics or cardiovascular risk management department with an eGFR between 15 and 60 ml/min/1,73m^2 within 30 days of their visit to the outpatient clinic. Patients were excluded when there was no available 24-hour urinary sodium excretion measure.

Ethics

This research is part of a previously allocated non-WMO approval from the regional Medical Ethics Committee.

Data Collection

We extracted the following information from UPOD: demographic characteristics; urinary sodium and protein excretion, eGFR, blood pressure, diabetes mellitus, medication use, all-cause mortality, and dialysis.

The day of the first available 24-hour urinary sodium excretion measure was set as the index date. The eGFR recorded closest to the urinary sodium measure was then selected as baseline eGFR. Baseline urinary protein excretion was defined as the amount of protein in the 24-hour urine sample that was collected the least days apart from the baseline 24-hour urinary sodium measure. Only protein excretion measures collected within one year of the sodium excretion measure were included.

Clinical hypertension was defined according to the International Society of Hypertension[19]. A patient was regarded as having hypertension when they had clinical hypertension (i.e, systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg) at the outpatient clinic visit or when they were chronic users of antihypertensives at their first 24-hour urinary sodium excretion measure (i.e. as any antihypertensive medication, used for seven consecutive days or longer, being on the medication list within 31 days of the index date).

To calculate BMI, patients' weight and height recorded closest to the date of inclusion were selected. Only weight measures recorded within two years of the index date were included. No time limit was employed for height measures. Patients were categorised as: underweight (BMI <18.5), normal weight (BMI 18.5 - 24.9), overweight (BMI 25-29.9) or obese (BMI => 30).

Sodium intake was estimated by measuring urinary sodium excretion in a 24-hour urine sample. The mean sodium excretion was calculated from all urine samples collected in the first year after inclusion to account for daily variability of sodium intake and excretion[20]. When only one measure was available, that single value was used. Sodium excretion was grouped into categories of 17 mmol, corresponding to 1 gram of sodium chloride[21]. Patients were categorised into the following groups: low sodium excretion (< 100 mmol/day or <2.3 grams of sodium or < 5.8 grams of sodium chloride), medium sodium excretion (100 – 200 mmol/day or 2.3 – 4.6 grams of sodium or 5.8 – 11.6 grams of salt) or high sodium excretion (>200 mmol/day or > 4.6 grams of sodium or > 11.6 grams of sodium chloride). Urinary sodium excretion was also

treated as a continuous variable. A daily sodium excretion of over 600 mmol was considered to be a measurement error/outlier.

Outcomes

All-cause mortality was defined as mortality censored before the UPOD data request. If no information on the vital status was available, the patients were censored alive at the point of last contact.

End-stage kidney disease (ESKD) was defined when at least one of the following statements were true: 1) patient required dialysis in the follow-up period; 2) patient underwent renal transplantation surgery; 3) eGFR was <15 ml/min/1,73m^2 for at least 90 consecutive days during follow-up; 4) the last recorded eGFR before follow-up ended was <15 ml/min/1,73m^2

Statistical Analyses

Normally distributed data were presented as mean with standard deviation (SD). Non-normal data was presented as median with interquartile range (IQR). Comparison of baseline variables between sodium excretion groups was done using the parametric non-paired T-test, Mann-Whitney U-test, one-way ANOVA, or Chi-square test when appropriate. To assess the relationship between 24-hour urinary sodium excretion as a categorical variable and all-cause mortality *or progression to ESKD*, Kaplan-Meier survival plots were created and stratified for CKD stage. Finally, all sodium excretion measures during follow-up were treated as a time-dependent variable in a Cox proportional hazards model. The logistic regression and Cox model were corrected for age, sex, baseline GFR, proteinuria, BMI, hypertension, and diabetes mellitus. Statistical testing was performed in RStudio (version 4.3.3). A p-value of <0.05 was considered significant.

Results

Baseline characteristics

There were 3787 patients (42.1% female) included with a mean age of 58.5 years (SD 15.0 years) and a mean BMI of 25.9 kg/m2 (SD 5.0) (Table 1). Median eGFR was 37 ml/min/1,73m^2 (IQR 20 - 54). Mean estimated sodium intake in the first year was 138.1 mmol/day (SD 93.6 mmol). Median urinary protein excretion was 0.6 g/day (IQR 0.2 - 1.8). In total, 677 patients (17.9%) had already received a kidney transplant.

The low sodium group contained less men (45.7%), had a lower median eGFR of 34 ml/min/1,73m^2 (IQR 20 - 52) and a higher mean age of 60.9 years (SD 14.8). Median eGFR was lowest in the low salt group at 34 (IQR 20 – 52), but so was median urinary protein excretion: 0.5 grams/day (IQR 0.2 – 1.4) It had the lowest mean BMI: 25.3 (SD 5.0) and the lowest systolic blood pressure: 135.3 (SD 25.1).

Sodium excretion

The mean sodium excretion in the first 24-hour urine was 137.8 (SD 92.7) mmol/day. Mean first-year sodium excretion was 132.9 (SD 71.8) mmol/day. A total of 19955 24-hour sodium excretion measures were available for 3789 patients. The median number of 24-hour urinary sodium excretion measures was 2 (IQR 1-6). The maximum number of 24-hour urinary sodium measures for one patient was 140. Most patients were classified as medium estimated sodium intake group at baseline (51.9%). The high sodium group was smallest (14.6%). When compared to the single baseline sodium measure, the first-year mean classifies 7.3% of low-intake, 21.5% of medium intake and 13.6% of high intake patients differently (Table 3).
Median follow-up was 3.30 years (IQR: 1.06 - 6.41 years), in which 1082 patients (28.6%) died during follow-up and 689 patients progressed to ESKD. Patients in the low estimated sodium intake group progressed to ESKD faster (median 1.7 years, IQR 0.3 – 4.7) than the medium (3.1 years, IQR 0.9 – 6.3) and high (3.1 years, IQR 1.0 – 6.1) estimated intake groups.

Survival analysis

Mortality rate was highest in the low sodium excretion group (38%) and lowest in the high sodium excretion group (22.3%) (Figure 1). Patients in the low sodium excretion group had a shorter median follow-up period of 2.52 years (IQR 0.70 - 5.44 years). Median time to death was shortest in the low sodium excretion group: 1.22 years (IQR 0.27 - 3.50 years). These results were consistent when stratifying for CKD stage at baseline: i.e. overall survival and survival time were lowest in the low estimated sodium intake group for every CKD stage (Figure 4).

Cox Proportional Hazards Model

When accounting for estimated sodium intake over time, the hazard ratio for every one-gram increase in estimated sodium intake was 0.95 (95% CI 0.93 - 0.98) when correcting for age, hypertension and diabetes (Table 4). The corrected hazard ratio for having a medium estimated sodium intake was 0.63 (95% CI 0.55 - 0.72) when compared to a low estimated sodium intake. The corrected hazard ratio for the high sodium intake was 0.68 (95% CI 0.55 - 0.83) when compared to a low estimated sodium intake.

Discussion

We found, in this large cohort of patients with CKD seen in routine clinical practice, that lower estimated sodium intake was associated with increased mortality risk and increased risk of progression to ESKD. However, there was no increase of mortality rate observed for patients with a very high estimated salt intake. Survival rates were similar for patients in all CKD stages, with lowest survival in the low sodium intake group. We found no changes when correcting or stratifying for eGFR or urinary protein excretion, implying that the correlation between sodium intake and mortality is independent of kidney function.

In addition, we concluded that adhering to thresholds of sodium intake according to guidelines is very difficult for patients with CKD. The Kidney Disease Improving Global Outcomes (KDIGO) workgroup recommends a maximum sodium chloride intake of 5 grams per day[8] for patients with CKD. This is in line with recommendations of leading health institutions like the World Health Organisation and the American Heart Association, which recommend a salt intake below six grams per day for the general population[22–24]. In the Netherlands, the median daily salt intake is 9.7 grams per day for men and 7.4 grams per day for women. 90 percent of men and 75 percent of women have a salt intake above the recommended amount of six grams, even though sodium content in processed foods has decreased in recent years[25]. In this cohort, less than 33.5% of patients had a sodium intake below the KDIGO guideline limit. While this does demonstrate the effect of the outpatient clinic visits with respect to reducing sodium intake, it still questions the feasibility of the current guidelines.

As in many other studies regarding dietary sodium intake, an intermediary measure was chosen to quantify the intake. Sodium excretion in a 24-hour collection urine sample is regarded to be the most accurate mode of measurement[26]. Under normal conditions, sodium is excreted through urine, sweat and the gastrointestinals[26]. In healthy individuals, 93 percent of this sodium is excreted in the urine[27], making urine analysis a reliable method of measurement. Sodium excretion is not a continuous process but follows a diurnal distribution, with excretion rates being highest around midday and just before waking up. Therefore, measuring sodium excretion over a 24-hour period is more accurate than a spot urine or night-time urine sample[26]. Finally, dietary recall questionnaires have been proven to systematically underestimate actual intake[26]. When multiple measures are available, calculating the mean sodium excretion over a minimum period of one year is regarded as the most accurate way to estimate intake because of day-to-day variation in both sodium excretion and diet[20,28.] . The multiple-measure average is widely used in contemporary literature[14,15,29].

We provided data based on almost 4000 patients in clinical practice, almost doubling the amount of currently available retrospective evidence in the non-dialysis CKD population[12,14–17]. Although a causal relationship could not be inferred, low sodium intake was clearly associated in our study with increased mortality rates, even after correcting for additional risk factors. Yet, residual confounding cannot be fully excluded. At the same time, this study does not prove a causal relationship between sodium intake and mortality. Information about important factors like overall food intake, comorbidity, physical activity, or frailty was not available, as this study is based on the information available in electronic healthcare records. Since salt intake is directly

correlated to total food intake[6], it is possible that low estimated salt intake resulted from low overall food intake, either intentionally to adhere to the guideline, or because of health issues reducing hunger, or because of reduced activity levels resulting in less caloric expenditure. The increased mortality could therefore be attributed to malnutrition or comorbidity instead of decreased sodium in the diet. In light of the retrospective nature of this study, drawing any conclusions about causality is hampered.

The ideal method to prove the link between sodium intake and mortality would be a number randomised prospective 'feeding' trials where dietary sodium intake was controlled by the researchers. Previous RCTs were mostly limited by a short follow-up, including a limited sample of patients, and focussing on surrogate outcomes (i.e. blood pressure) as opposed to mortality or morbidity. RCT with a dietary regimen can only be maintained for short time periods in a small number of participants[30], not only because of the organisational and financial burden of this research, but also from an ethical point of view. This, however, does not mean that we cannot challenge sodium restriction as a treatment; since there is also no available high-grade evidence supporting it. Future research should investigate the patient characteristics that make patients with CKD more susceptible to the effects of dietary sodium, both adverse and protective.

Conclusion

Patients in this cohort who had a low sodium intake, as recommended by global guidelines, had a higher mortality rate and shorter survival time than patients with higher sodium intakes. The results of this study call for a more personalised approach to dietary intervention in CKD patients and question the need of sodium restriction for all.

Appendix

Table 1. Baseline characteristics

Sodium Intake Group		Low (<100mmol/day)	Medium (100-200 mmol/day)	High (>200 mmol/day)	Total	p
Number of patients	n (%)	1268 (33.5)	1966 (51.9)	553 (14.6)	3787	
Female	n (%)	689 (54.3)	755 (38.4)	151 (27.3)	1595 (42.1)	<0.001
Age	Mean (SD)	60.9 (14.8)	57.9 (15.0)	54.9 (14.8)	58.5 (15.0)	<0.001
eGFR	Median (IQR)	34.0 (20.0 to 52.0)	37.0 (20.0 to 53.9)	45.0 (23.0 to 60.0)	37.0 (20.0 to 54.0)	<0.001
CKD stage	1	38 (3.0)	41 (2.1)	32 (5.8)	111 (2.9)	<0.001
	2	163 (12.9)	281 (14.3)	116 (21.0)	560 (14.8)	
	3a	249 (19.7)	430 (21.9)	132 (23.9)	811 (21.4)	
	3b	252 (19.9)	463 (23.6)	88 (15.9)	803 (21.2)	
	4	523 (41.3)	690 (35.1)	170 (30.8)	1383 (36.6)	
	5	40 (3.2)	59 (3.0)	14 (2.5)	113 (3.0)	
Urinary Protein Excretion	Median (IQR)	0.5 (0.2 to 1.4)	0.7 (0.2 to 1.9)	0.9 (0.3 to 2.4)	0.6 (0.2 to 1.8)	<0.001
Systolic Blood Pressure	Mean (SD)	135.3 (25.1)	139.3 (23.8)	136.4 (23.4)	137.5 (24.3)	<0.001
Diastolic Blood Pressure	Mean (SD)	77.4 (14.2)	81.0 (14.1)	80.3 (14.3)	79.7 (14.3)	<0.001
Hypertension	n (%)	1019 (83.7)	1641 (87.6)	429 (81.2)	3089 (85.4)	<0.001
Antihypertensive Medication	n (%)	921 (72.6)	1495 (76.0)	388 (70.2)	2804 (74.0)	0.008
Diuretic	n (%)	531 (41.9)	764 (38.9)	191 (34.5)	1486 (39.2)	0.011
RAS-inhibitor	n (%)	482 (38.0)	935 (47.6)	241 (43.6)	1658 (43.8)	<0.001
Other	n (%)	695 (54.8)	1130 (57.5)	283 (51.2)	2108 (55.7)	0.023
Diabetes	n (%)	513 (40.5)	750 (38.1)	236 (42.7)	1499 (39.6)	0.116
BMI	Mean (SD)	25.3 (5.0)	26.2 (4.9)	26.4 (5.0)	25.9 (5.0)	0.001
RTx at baseline	n (%)	218 (17.2)	366 (18.6)	93 (16.8)	677 (17.9)	0.458

eGFR: estimated glomerular filtration rate (ml/min/1,73m^2). CKD: chronic kidney disease. BMI: body mass index. RTx : renal transplantation.

Table 2. Mortality and progression to ESKD

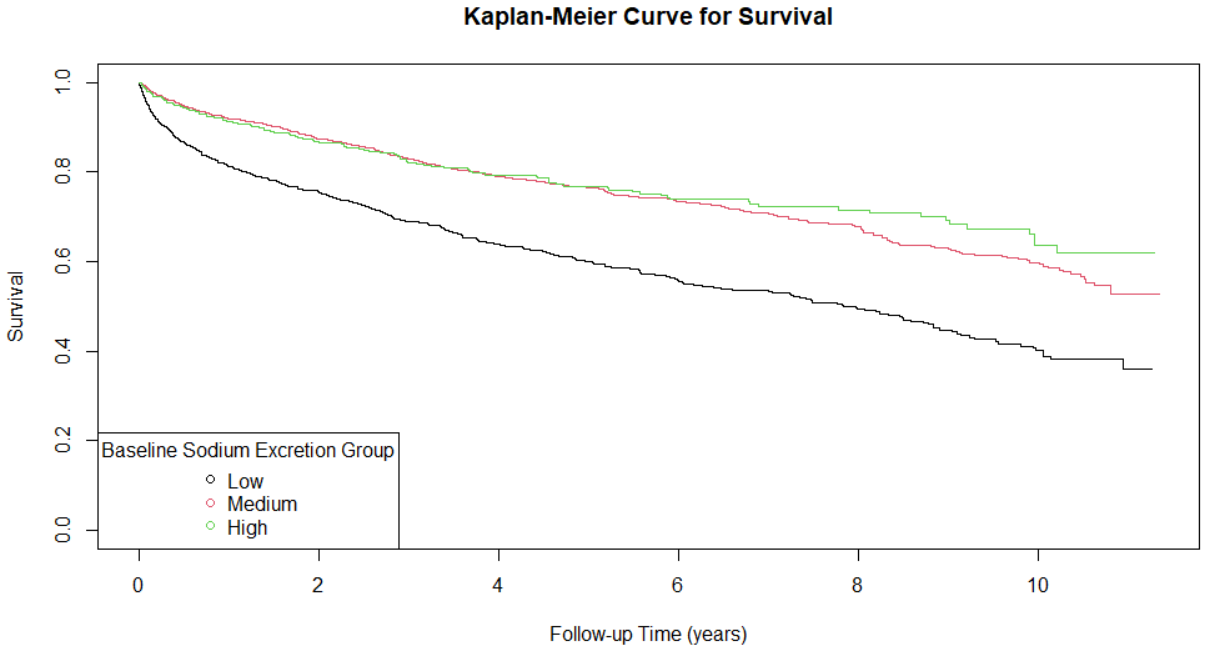
Sodium Intake Group		Low (<100mmol/day)	Medium (100-200 mmol/day)	High (>200 mmol/day)	Total	p
Follow-up Time (years)	Median (IQR)	2.5 (0.7 to 5.4)	3.7 (1.4 to 6.8)	3.7 (1.4 to 6.8)	3.3 (1.1 to 6.4)	<0.001
Urinary Sodium Excretion (mmol/day)	Mean (SD)	62.7 (26.2)	142.9 (27.4)	258.0 (61.0)	132.9 (71.8)	<0.001
Deceased	n (%)	482 (38.0)	476 (24.2)	122 (22.1)	1080 (28.5)	<0.001
Years to Death	Median (IQR)	1.2 (0.3 to 3.5)	2.3 (0.7 to 4.7)	1.8 (0.5 to 3.7)	1.8 (0.4 to 4.0)	<0.001
ESKD	n (%)	286 (22.6)	327 (16.6)	76 (13.7)	689 (18.2)	<0.001
Years to ESKD	Median (IQR)	1.7 (0.3 to 4.7)	3.1 (0.9 to 6.3)	3.1 (1.0 to 6.1)	2.7 (0.6 to 5.7)	<0.001
Dialysis	n (%)	224 (17.7)	226 (11.5)	52 (9.4)	502 (13.3)	<0.001
NTx	n (%)	55 (4.3)	89 (4.5)	21 (3.8)	165 (4.4)	0.758

Table 3. Classification of patients based on: first 24-hour urinary sodium excretion, first-year mean urinary sodium excretion and mean of all urinary sodium excretion measures.

Sodium Excretion Group		Low	Medium	High	Total
Number of patients	n (%)	1268 (33.5)	1966 (51.9)	553 (14.6)	3787
First 24-hour USE (mmol/day)	Mean (SD)	61.8 (39.6)	149.7 (63.4)	269.5 (99.2)	137.8 (92.7)
Grouped by first 24-h USE: n (%)	Low	1175 (92.7)	213 (10.8)	16 (2.9)	1404 (37.1)
	Medium	82 (6.5)	1543 (78.5)	59 (10.7)	1684 (44.5)
	High	11 (0.9)	210 (10.7)	478 (86.4)	699 (18.5)

24-h USE: 24-hour urinary sodium excretion.

Figure 1. Kaplan Meier Survival Analysis



Number at risk	0-2	2-4	4-6	6-8	8-10	>10
Low	1265	722	448	275	168	74
Medium	1962	1356	923	608	358	159
High	551	376	235	161	103	51

Table 4. Cox proportional hazards model for survival.

Table 4a. Hazard ratio for increased estimated intake of 1g of sodium chloride per day.

	Hazard ratio	95% CI	p
Crude (estimated intake in grams of salt per day)	0.9388	0.9184 - 0.9597	<0.001
Corrected for patient characteristics[1]	0.953	0.9313 - 0.9753	<0.001
Corrected for renal factors[2]	0.9420	0.9194 - 0.9650	<0.001
Corrected for cardiovascular factors[3]	0.9360	0.9109 - 0.9619	<0.001
Corrected for all significant confounders[4]	0.9547	0.9342 - 0.9756	<0.001

Table 4b. Cox proportional hazards model for survival. Hazard ratio compared to low sodium intake group.

	Intake group	Hazard ratio	95% CI	p
Crude:	Medium	0.56094	0.4904 - 0.6416	<0.001
	High	0.55713	0.4558 - 0.6810	<0.001
Corrected for patient characteristics[1]	Medium	0.5957	0.5195 - 0.6830	<0.001
	High	0.6767	0.5504 - 0.8319	<0.001
Corrected for renal factors[2]	Medium	0.5642	0.4880 - 0.6523	<0.001
	High	0.5715	0.4586 - 0.7122	<0.001
Corrected for cardiovascular factors[3]	Medium	0.5854	0.4872 - 0.7035	<0.001
	High	0.5416	0.4142 - 0.7082	<0.001
Corrected for significant confounders[4]	Medium	0.6301	0.5497 - 0.7223	<0.001
	High	0.6755	0.5496 - 0.8302	<0.001

1: Age & sex
2: eGFR & urinary protein excretion
3: Hypertension, diabetes & BMI
4: Age, hypertension, diabetes

Figure 3. Hazard Ratios from Crude Cox Proportional Hazards Model with Time-varying Covariates.

Reference category: Estimated daily salt intake of 5 grams.

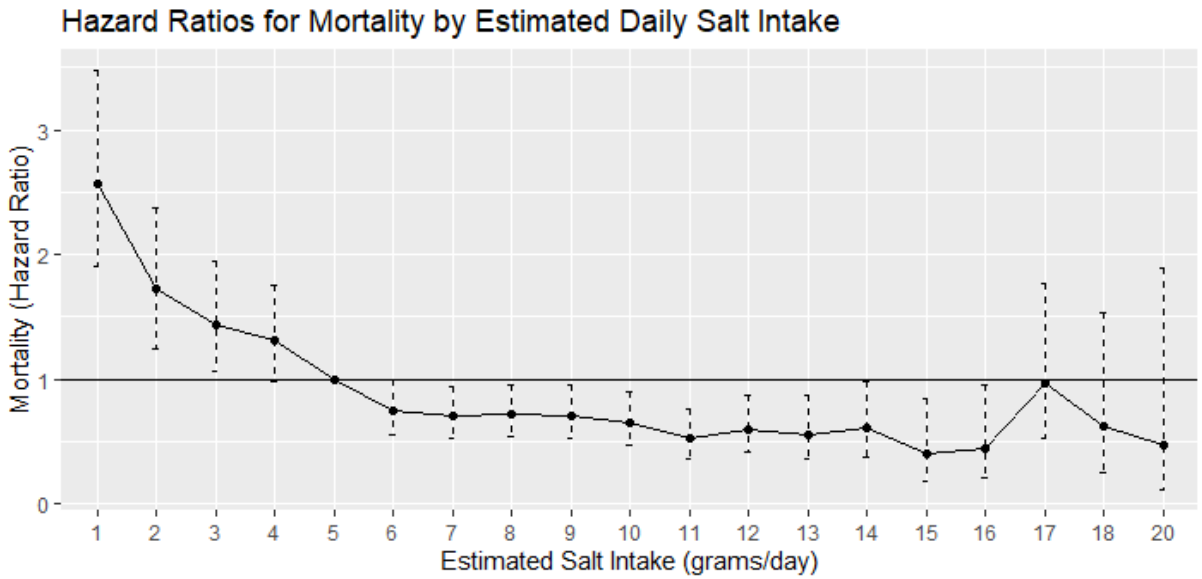


Figure 4. Kaplan Meier survival analysis stratified per CKD stage at baseline.

Figure 4a.

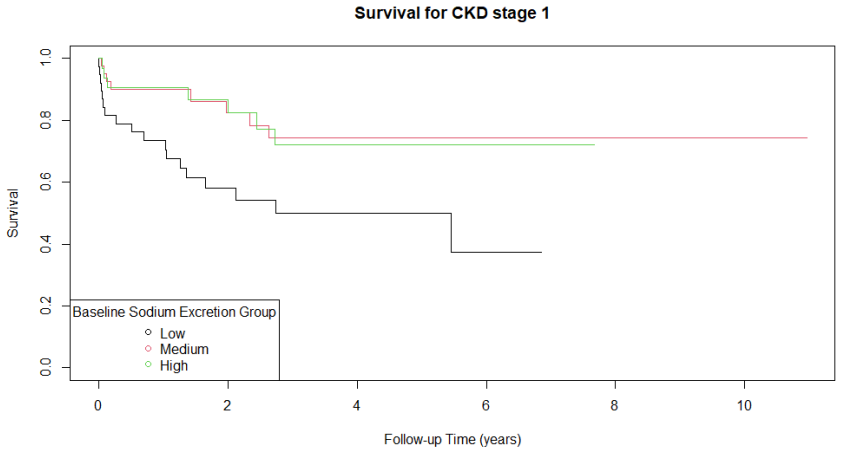
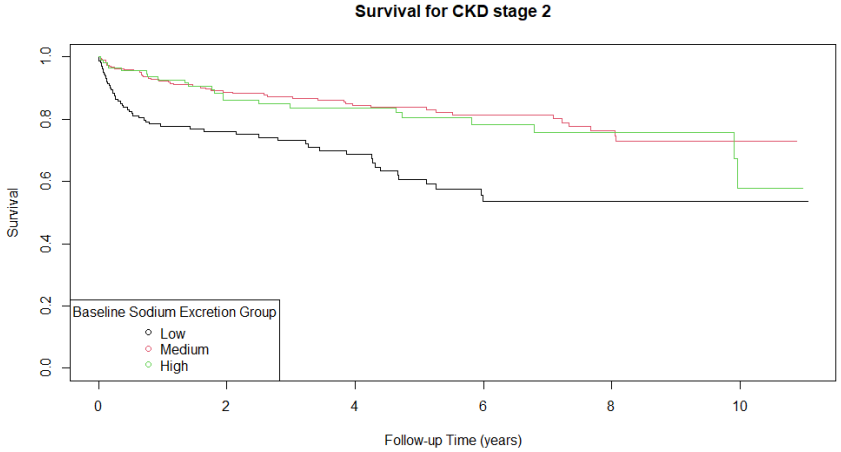


Figure 4b



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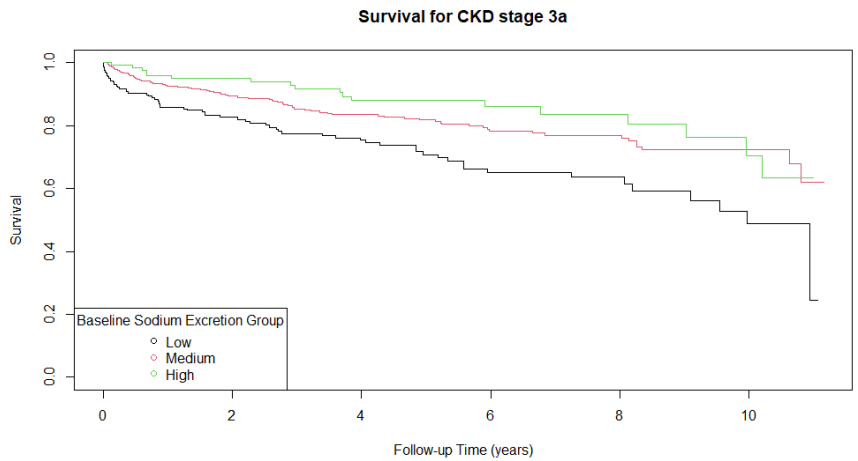

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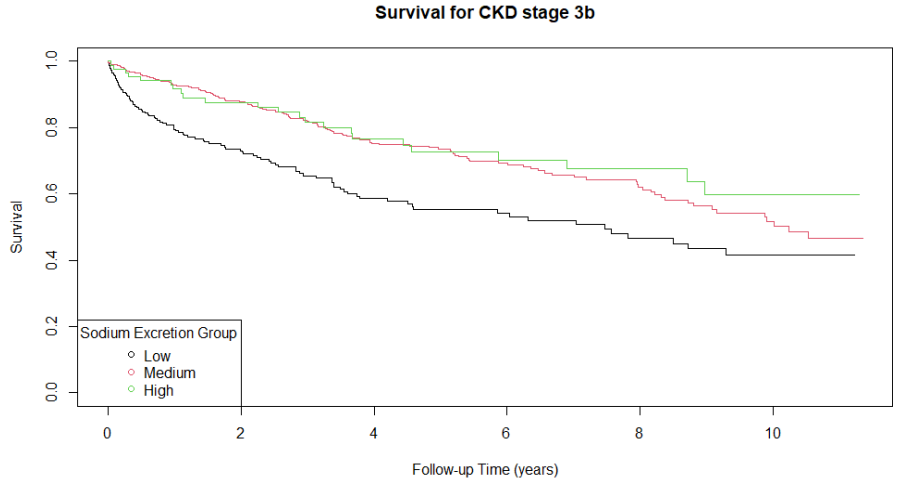

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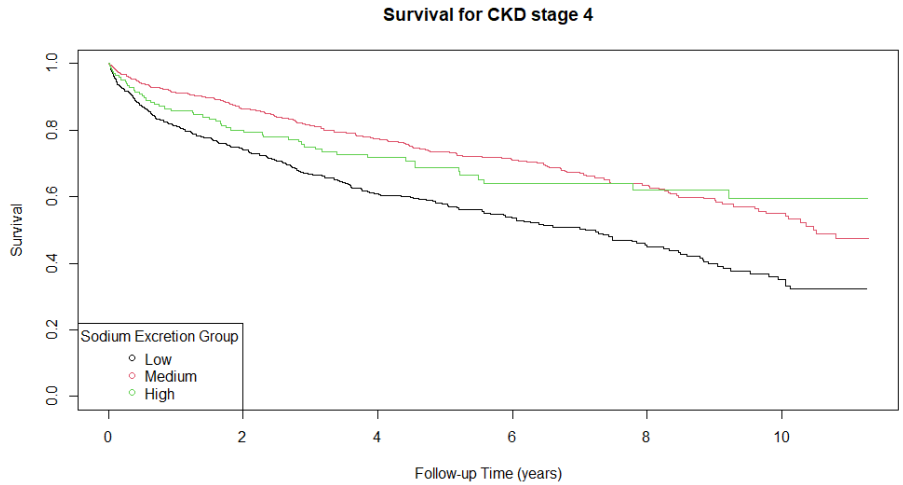
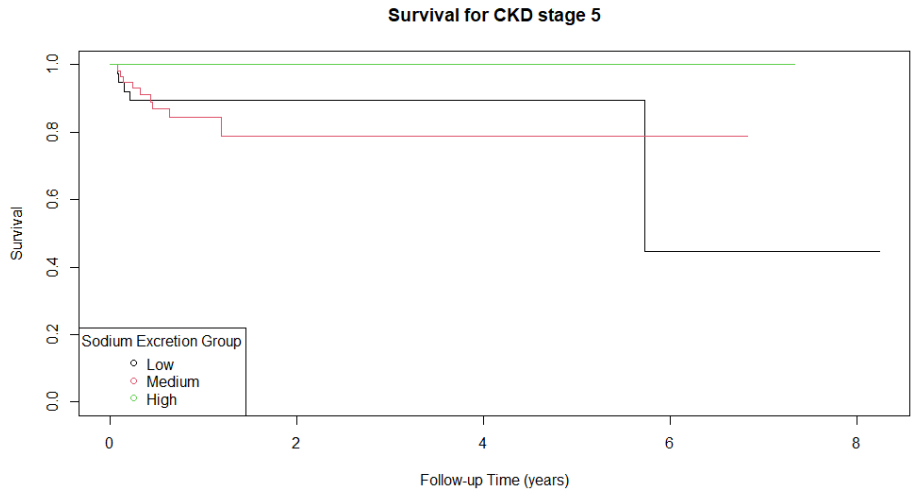


Figure 4f



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